Shock 2017 military supplement an overview of two human trials of perfluorocarbon emulsions in non-cardiac surgery

Spahn, Donat R ; Keipert, Peter E

Abstract: Perfluorochemicals (PFCs) constitute one class of artificial oxygen carriers that are being produced completely synthetically. One formulation that has been evaluated extensively in clinical trials is a 60% w/v perflubron-based emulsion. Efficacy and safety of this perflubron emulsion was evaluated in a Phase 2 and a large prospective randomized Phase 3 multicenter European study, which collectively included a total of 639 patients. Perflubron emulsion was highly successful in improving organ function, reversing physiologic transfusion triggers and in reducing the need for allogeneic blood transfusions. There were no major safety issues.

DOI: https://doi.org/10.1097/SHK.0000000000000986

Shock, Publish Ahead of Print

DOI : 10.1097/SHK.0000000000000986

SHOCK 2017 MILITARY SUPPLEMENT

An overview of Two Human Trials of Perfluorocarbon Emulsions in Non-Cardiac Surgery

Donat R. Spahn[1] and Peter E. Keipert [2]

[1] Professor and Chairman, Institute of Anesthesiology, University and University Hospital of Zurich, Zurich, Switzerland

[2] President, KEIPERT Corp. Life Sciences Consulting, San Diego, CA USA

Address for correspondence:

Donat R. Spahn, MD, FRCA
Professor and Chairman
Institute of Anesthesiology
Section Head
Anesthesiology - Intensive Care Medicine - OR-Management
University of Zurich and University Hospital Zurich
Raemistrasse 100
CH-8091 Zurich, Switzerland

Phone: +41 44 255 2695
FAX: +41 44 255 9593

E-Mail: donat.spahn@usz.ch

Short title: Perfluorocarbon emulsions in non-cardiac surgery

Abstract

Perfluorochemicals (PFCs) constitute one class of artificial oxygen carriers that are being produced completely synthetically. One formulation that has been evaluated extensively in clinical trials is a 60% w/v perflubron-based emulsion. Efficacy and safety of this perflubron emulsion was evaluated in a Phase 2 and a large prospective randomized Phase 3 multicenter European study, which collectively included a total of 639 patients. Perflubron emulsion was highly successful in improving organ function, reversing physiologic transfusion triggers and in reducing the need for allogeneic blood transfusions. There were no major safety issues.

Keywords: Artificial oxygen carrier, Surgery, Anemia,Transfusion, Patient Blood Management, Perfluorocarbons

Patient Blood Management (PBM)(17-19, 22) has been developed to avoid the adverse effects of preoperative anemia(11), preoperative iron deficiency (10), high blood loss (12) and the transfusion of allogeneic blood products(1, 4, 5, 18)on patient outcome.

Within the concept of PBM, acute normovolemic hemodilution (ANH) is one of the measures contributing to reduce the need for allogeneic blood products (18, 19, 22). The efficacy of mild ANH, however, has been challenged (2) and profound ANH exposes the patient to low hemoglobin levels that may not be well tolerated by certain patient groups. Therefore, the concept of augmented ANH was developed to combine ANH with the administration of an artificial oxygen (O2) carrier in order to maintain O2 supply to vulnerable organs during the period of minimal Hb(3, 8). Perfluorochemicals (PFCs) constitute one class of artificial oxygen carriers with the advantage of being produced completely synthetically(13). The formulation that has been evaluated extensively in Western Europe and North America in clinical trials is a 60% w/v perflubron-based emulsion originally developed by Alliance Pharmaceutical (San Diego, CA), which is a lecithin-stabilized emulsion of perfluorooctyl bromide ($C_8F_{17}Br$) and perfluorodecyl bromide ($C_{10}F_{21}Br$)(7). Efficacy and safety of this perflubron emulsion was first evaluated in a Phase 2 study in Europe(20)and subsequently in a large prospective randomized, Phase 3 multicenter European study performed in 492non-cardiac surgery patients(21).

The European Phase 2 study enrolled 147 patients undergoing major orthopedic surgery(20). All patients underwent ANH to a Hb of 90 g/L immediately prior to surgery while being ventilated with an inspiratory O2 fraction (FiO_2) of 0.40. The volume of the autologous blood harvested on average was approximately 1000 mL. When reaching a predefined physiologic transfusion trigger (Table 1A) patients were randomized to one of four treatment groups, as shown below.

(A) Re-transfusion of autologous blood (450 mL) harvested during ANH at FiO_2 of 0.40
(B) 450 mL of colloid at FiO_2 of 1.0
(C) 0.9 g perflubron emulsion per kg of body weight with colloid for a total volume of 450 mL at FiO_2 of 1.0
(D) 1.8 g perflubron emulsion per kg of body weight with colloid for a total volume of 450 mL at FiO_2 of 1.0

The protocol-defined primary endpoint was the duration of transfusion trigger reversal(20). In patients not achieving a transfusion trigger reversal or when reaching a transfusion trigger a

second time, one unit (450 mL) of autologous blood was re-transfused. All remaining autologous blood was re-transfused at the end of surgery.A Hb < 60 g/L after the first treatment,or a Hb < 80 g/L at the end of surgery were additional triggers for transfusion for autologous units first, followed by transfusion of allogeneic blood transfusions if needed to correct the Hb-based trigger.

High dose perflubron emulsion was the most successful treatment with a duration of transfusion trigger reversal of 80 (60 – 100) min (median (confidence interval)), followed by low dose perflubron emulsion (59 (40 – 90) min), re-transfusion of autologous blood (55 (30 – 70) min) and colloid only administration (30 (27 – 60) min). The duration of transfusion trigger reversal was significantly longer ($p < 0.05$) in both perflubron emulsion groups as compared to the colloid group. Furthermore, the duration of transfusion trigger reversal was significantly longer ($p < 0.05$) in the high dose perflubron emulsion group as compared to the autologous blood re-transfusion group. In addition, the percentage of transfusion trigger reversal was highest with high dose perflubron emulsion (97%, $p < 0.05$ vs. colloid and autologous blood re-transfusion groups), followed by low dose perflubron emulsion (82%), colloid only administration (76%) and re-transfusion of autologous blood (60%). The success of high-dose perflubron emulsion treatment tended to be underestimated. In more than 50% of patients, the true duration of transfusion trigger delay was artificially limited because the end of surgery, by protocol,mandated reinfusion of ANH blood and this occurred before a true transfusion trigger had been reached. This means that the true length of delay from tachycardia, hypotension, oxygen demand etc. could well have been considerably longer(20).

Allogeneic transfusions were similar in all treatment groups. This was to be expected for this study, since patients were managed at nearly identical Hb levels by protocol. In addition, the additional transfusion triggers of Hb < 60 g/L during the treatment and Hb < 80 g/L at the end of surgery virtually precluded a difference in allogeneic blood transfusions. If exclusively physiologic transfusion triggers would have been used, patients receiving high dose perflubron emulsion would be expected to tolerate lower Hb values; hence, bleeding would have occurred at lower Hb levels and thereby reduce red blood cell loss during surgery, which likely would have translated into a reduced need for allogeneic blood transfusions.

Treatment with perflubron emulsion was well tolerated, incidence of serious as well as all adverse events (AEs), and postoperative recovery was similar in all groups. The only difference was that on postoperative day 2-4 the platelet count was slightly lower in the high-dose perflubron emulsion group than in the other groups. However, the clinical relevance of this finding is likely to be minimal since it was not associated with any bleeding complication and may even be considered protective given that fact that in this period after major surgery (16) or trauma (14, 15) patients show signs of severe hyper-coagulopathy which may be associated with thrombotic complications.

In a subsequent prospective randomized multicenter Phase 3 study (492 patients in 34 centers in 8 countries),perflubron emulsion was tested in major non-cardiac surgery with an expected blood loss of ≥ 20 mL per kilogram of body weight(21). Patients randomized to the perflubron emulsion group were preoperatively hemodiluted to a target Hb of 80±5 g/L, and then received the first dose of perflubron emulsion (1.8 g per kg of body weight). When Hb reached 65±5 g/L, a second dose of perflubron emulsion (0.9 g per kg of body weight) was administered and RBC transfusion were then given as needed, eitherwhen Hb decreased to < 55±5 g/L or at protocol-defined physiologic transfusion triggers (Table 1B). Patients randomized into the control group were treated according to standard of care, which did not include preoperative hemodilution. During surgery these patients were transfused at a Hb < 80±5 g/L or at protocol-defined physiologic transfusion triggers (Table 1B). Postoperatively, a Hb transfusion trigger of 85±5 g/L was used in both groups. The primary outcome was the number of allogeneic and preoperative autologous units transfused and the percentage of patients avoiding any RBC transfusion(21).

More patients in the perflubron emulsion group avoided any RBC transfusion at 24h (53% vs. 43%, p=0.05) and fewer RBC transfusions were given (0 vs. 1 unit, p=0.013). At hospital discharge, these differences were still present but were no longer statistically different. However, in the protocol-defined target population, i.e.,in patients with a blood loss of ≥ 20 mL per kg of body weight (330 of 492 subjects), significantly more patients in the perflubron emulsion group avoided any RBC transfusion until hospital discharge (26% vs. 16%, p<0.05). In addition, the number of RBC units transfused was also lower in patients in the perflubron group than in control patients (2 vs. 4 units, p< 0.001).Overall, adverse events were similar in both groups,

while serious adverse events were more frequent in the perflubron emulsion group (32% vs. 21%, $p<0.05$).

Interestingly, a post-hoc exploratory analysis showed that in patients with a blood loss of ≥ 10 mL per kg of body weight (424 of 492 subjects), more patients could avoid any RBC transfusion when treated with ANH and perflubron emulsion than in control patients with standard of care treatment.

As seen in the previous Phase 2 study(20), postoperative platelet count was significantly lower in patients treated by perflubron emulsion for up to 7 days. However, the group mean platelet counts never reached a level below 100,000 / □l and was not associated with any bleeding complications or the need for supplemental treatment with fresh frozen plasma (13% in both groups) or platelet transfusion (7 platelet transfusions in each group)(21). This was consistent with the Phase 1 study of Leese et al. (9)who found various coagulation tests largely unaffected over 14 days in healthy volunteers following treatment with saline and perflubron emulsion at 1.2 and 1.8 g per kilogram of body weight.

Taken together, these two studies clearly show that the treatment with preoperative ANH and perflubron emulsion can reduce the need for allogeneic blood transfusion significantly in patients undergoing major non-cardiac surgery with a minimum blood loss of at least 10 mL per kg of body weight. The only consistent side effect observed was a lower platelet count during the first 7 days. It is very important to state that in both studies, postoperative platelet counts were well above 100,000 / □l and that no coagulopathic bleeding complications occurred. In fact, a mild decrease in postoperative platelet count might even protect against postoperative thrombo-embolic complications (14-16).

Besides the use to minimize the need for allogeneic RBC transfusions, perflubron emulsion has been evaluated as a potential oxygen therapeutic agent in a number of situations (Table 2) where ischemia can compromise tissue oxygenation and lead to potential organ injury and/or failure.Many of the preclinical studies performed to support these anti-ischemic indications have been published and described in various review articles(6, 7).Collectively, these studies have demonstrated that: (1) perflubron emulsion can support tissue oxygenation, (2) the oxygen

delivered by the PFC is available to support cellular metabolism at the tissue level, and (3) this improved oxygenation status has been shown to result in improved organ function.

References

1. Baharoglu MI, Cordonnier C, Al-Shahi Salman R, de Gans K, Koopman MM, Brand A, Majoie CB, Beenen LF, Marquering HA, Vermeulen M, Nederkoorn PJ, de Haan RJ, Roos YB, and Investigators P. Platelet transfusion versus standard care after acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH): a randomised, open-label, phase 3 trial. *Lancet* 387: 2605-2613, 2016.
2. Bryson GL, Laupacis A, and Wells GA. Does acute normovolemic hemodilution reduce perioperative allogeneic transfusion? A meta-analysis. The International Study of Perioperative Transfusion. *Anesth-Analg* 86: 9-15, 1998.
3. Cernaianu AC, Spence RK, Vassilidze TV, Gallueci JG, Gaprindashvili T, Olah A, Weiss RL, Cilley JH, Keipert PE, Faithfull NS, and DelRossi AJ. Improvement in circulatory and oxygenation status by perflubron emulsion (Oxygent HT) in a canine model of surgical hemodilution. *Artif Cells Blood Substit Immobil Biotechnol* 22: 965-977, 1994.
4. Chai-Adisaksopha C, Hillis C, Siegal DM, Movilla R, Heddle N, Iorio A, and Crowther M. Prothrombin complex concentrates versus fresh frozen plasma for warfarin reversal. A systematic review and meta-analysis. *Thrombosis and haemostasis* 116: 879-890, 2016.
5. Desborough M, Sandu R, Brunskill SJ, Doree C, Trivella M, Montedori A, Abraha I, and Stanworth S. Fresh frozen plasma for cardiovascular surgery. *Cochrane Database Syst Rev* 7: Cd007614, 2015.
6. Flaim SF. Efficacy of perflubron-based emulsion as a temporary oxygen carrier. In: *Red Blood Cell Substitutes: Basic Principles and Clinical Applications*, edited by Rudolph AS, Rabinovici R and Feuerstein GZ: Marcel Dekker, Inc., New York, 1998, p. 79-117.
7. Keipert PE. Oxygent™, a Perfluorochemical-Based Intravascular Oxygen Therapeutic for Surgical Patients. In: *Blood Substitutes*, edited by Winslow RM: Elsevier, Academic Press (Lodon), 2006, p. 312-323.
8. Keipert PE and Stehling L. The concept of augmented acute normovolemic hemodilution: Using a perfluorochemical-based intravenous oxygen carrier to decrease allogeneic blood transfusion in elective surgery. *Transfusion Alternatives in Transfusion Med (TATM)* 3: 11-16, 2001.
9. Leese PT, Noveck RJ, Shorr JS, Woods CM, Flaim KE, and Keipert PE. Randomized safety studies of intravenous perflubron emulsion. I. Effects on coagulation function in healthy volunteers. *Anesthesia and analgesia* 91: 804-811., 2000.
10. Munoz M, Acheson AG, Auerbach M, Besser M, Habler O, Kehlet H, Liumbruno GM, Lasocki S, Meybohm P, Rao Baikady R, Richards T, Shander A, So-Osman C, Spahn DR, and Klein AA. International consensus statement on the peri-operative management of anaemia and iron deficiency. *Anaesthesia* 72: 233-247, 2017.
11. Musallam KM, Tamim HM, Richards T, Spahn DR, Rosendaal FR, Habbal A, Khreiss M, Dahdaleh FS, Khavandi K, Sfeir PM, Soweid A, Hoballah JJ, Taher AT, and Jamali FR. Preoperative anaemia and postoperative outcomes in non-cardiac surgery: a retrospective cohort study. *Lancet* 378: 1396-1407, 2011.
12. Ranucci M, Baryshnikova E, Castelvecchio S, and Pelissero G. Major bleeding, transfusions, and anemia: the deadly triad of cardiac surgery. *The Annals of thoracic surgery* 96: 478-485, 2013.
13. Riess JG. Understanding the fundamentals of perfluorocarbons and perfluorocarbon emulsions relevant to in vivo oxygen delivery. *Artif Cells Blood Substit Immobil Biotechnol* 33: 47-63, 2005.

14. Schlimp CJ, Ponschab M, Voelckel W, Treichl B, Maegele M, and Schochl H. Fibrinogen levels in trauma patients during the first seven days after fibrinogen concentrate therapy: a retrospective study. *Scand J Trauma Resusc Emerg Med* 24: 29, 2016.
15. Schochl H, Voelckel W, Maegele M, Kirchmair L, and Schlimp CJ. Endogenous thrombin potential following hemostatic therapy with 4-factor prothrombin complex concentrate: a 7-day observational study of trauma patients. *Crit Care* 18: R147, 2014.
16. Solomon C, Hagl C, and Rahe-Meyer N. Time course of haemostatic effects of fibrinogen concentrate administration in aortic surgery. *British journal of anaesthesia* 110: 947-956, 2013.
17. Spahn DR. Patient Blood Management: the new standard. *Transfusion* 57: 1325-1327, 2017.
18. Spahn DR and Goodnough LT. Alternatives to blood transfusion. *Lancet* 381: 1855-1865, 2013.
19. Spahn DR, Moch H, Hofmann A, and Isbister JP. Patient blood management: the pragmatic solution for the problems with blood transfusions. *Anesthesiology* 109: 951-953, 2008.
20. Spahn DR, van Bremt R, Theilmeier G, Reibold JP, Welte M, Heinzerling H, Birck K, Keipert PE, Messmer K, and Perflubron Emulsion Study Group. Perflubron emulsion delays blood transfusion in orthopedic surgery. *Anesthesiology* 91: 1195-1208, 1999.
21. Spahn DR, Waschke K, Standl T, Motsch J, van Huynegem L, Welte M, Gombotz H, Coriat P, Verkh L, Faithfull NS, Keipert P, and and the European Perflubron Emulsion in Non-Cardiac Surgery Study Group. Use of perflubron emulsion to decrease allogeneic blood transfusion in high-blood loss non-cardiac surgery: results of a European phase 3 study. *Anesthesiology* 97: 1338-1349, 2002.
22. Williamson LM and Devine DV. Challenges in the management of the blood supply. *Lancet* 381: 1866-1875, 2013.

Table 1: Physiologic transfusion triggers in (A) Study in major orthopedic surgery (n=147) (20) and (B) Study in major non-cardiac surgery (n=492) (21).

A – Major orthopedic surgery (n=147)

Tachycardia: HR > 125% of HR after ANH or HR > 110 bpm

Hypotension: MAP < 75% of MAP after ANH or MAP ≤ 60 mmHg

High cardiac output: CO > 150% of CO after ANH

High O2 extraction: PmvO2 < 38 mmHg

B – Major non-cardiac surgery surgery (n=492)

Tachycardia: HR > 135% of HR after anesthesia induction or HR > 100 bpm

Hypotension: MAP < 65% of MAP after anesthesia induction or MAP ≤ 60 mmHg

High O2 extraction: PmvO2 < 38 mmHg (if PA catheter inserted)

ST segment alteration: ST depression > 0.1 mV or elevation > 0.2 mV

HR = heart rate, ANH = acute normovolemic hemodilution, MAP = mean arterial pressure, CO = cardiac output, PmvO2 = O2 partial pressure in mixed venous blood, PA catheter = Pulmonary artery catheter.

Table 2: Potential use of perflubron emulsion outside the paradigm of blood sparing and Patient Blood Management.

Urgent need for improved O2 delivery
Ambulance
Emergency room
Jehovah Witness patients
Bridge to transfusion
Cardiac ischemia
CPB
PCI
MI
Cerebral ischemia
Aneurysm
Stroke
CPB
Gut ischemia
Intensive care treatment
Abdominal surgery
CPB
Trauma / shock resuscitation
Sickle cell crisis
Tumor oxygenation prior to radiation / chemotherapy
Organ preconditioning for transplantation

Conflict-of-interest statement (past 5 years): Donat R. Spahn

Dr. Spahn's academic department is / has been receiving grant support from the Swiss National Science Foundation, Berne, Switzerland, the Ministry of Health (Gesundheitsdirektion) of the Canton of Zurich, Switzerland for Highly Specialized Medicine, the Swiss Society of Anesthesiology and Reanimation (SGAR), Berne, Switzerland, the Swiss Foundation for Anesthesia Research, Zurich, Switzerland, Bundesprogramm Chancengleichheit, Berne, Switzerland, CSL Behring, Berne, Switzerland, Vifor SA, Villars-sur-Glâne, Switzerland.

Dr. Spahn is the co-chair of the ABC-Trauma Faculty, managed by Physicians World Europe, Mannheim, Germany and sponsored by unrestricted educational grants from Novo Nordisk Health Care AG, Zurich, Switzerland, CSL Behring GmbH, Marburg, Germany and LFB Biomédicaments, Courtaboeuf Cedex, France.

In the past 5 years, Dr. Spahn has received honoraria or travel support for consulting or lecturing from: Danube University of Krems, Austria, US Department of Defense, Washington, USA, Abbott AG, Baar, Switzerland, AMGEN GmbH, Munich, Germany, AstraZeneca AG, Zug, Switzerland, Baxter AG, Volketswil, Switzerland,Baxter S.p.A., Roma, Italy, Bayer, Zürich, Switzerland and Berlin, Germany, B. Braun Melsungen AG, Melsungen, Germany, Boehringer Ingelheim (Schweiz) GmbH, Basel, Switzerland, Bristol-Myers-Squibb, Rueil-Malmaison Cedex, France and Baar, Switzerland, CSL Behring GmbH, Hattersheim am Main, Germany and Berne, Switzerland, Curacyte AG, Munich, Germany, Daiichi Sankyo (Schweiz) AG, Thalwil, Switzerland, Ethicon Biosurgery, Sommerville, New Jersey, USA, Fresenius SE, Bad Homburg v.d.H., Germany, Galenica AG, Bern, Switzerland (including Vifor SA, Villars-sur-Glâne, Switzerland),GlaxoSmithKline GmbH & Co. KG, Hamburg, Germany, Haemonetics, Braintree, MA, USA, Janssen-Cilag, Baar, Switzerland and Beerse, Belgium, LFB Biomédicaments, Courtaboeuf Cedex, France, Merck Sharp & Dohme AG, Luzern, Switzerland, Novo Nordisk A/S, Bagsvärd, Denmark, Octapharma AG, Lachen, Switzerland, Organon AG, Pfäffikon/SZ, Switzerland, PAION Deutschland GmbH, Aachen, Germany, Pharmacosmos A/S, Holbaek, Denmark, Photonics Healthcare B.V., Utrecht, Netherlands, ratiopharm Arzneimittel Vertriebs-GmbH, Vienna, Austria, Roche, Reinach, Switzerland, Sarstedt AG & Co., Sevelen, Switzerland and Nümbrecht, Germany, Schering-Plough International, Inc., Kenilworth, New Jersey, USA, Tem International GmbH, Munich, Germany, Verum Diagnostica GmbH, Munich, Germany, Vifor Pharma, Munich, Germany, Vienna, Austria and St. Gallen, Switzerland.

Conflict-of-interest statement (past 5 years): Peter E. Keipert

During the conduct of the clinical studies with perflubron emulsion described in this paper, Dr. Keipert was employed by Alliance Pharmaceutical as the Program Director responsible for overseeing the preclinical and clinical development of perflubron emulsion, until Alliance had to terminate operations in 2002. Over the past 5 years, Dr. Keipert has worked as an independent consultant in this field as founder and President of KEIPERT Corp. Life Sciences Consulting (San Diego, CA). In this capacity, Dr. Keipert has received consulting fees from CymBlood, Ltd at the University of Essex (Colchester, UK), and from Prolong Pharmaceuticals (South Plains, NJ) for work to support their Hb-based oxygen carrier (HBOC) development. From 2004 to 2013, Dr. Keipert was also employed by Sangart Inc. (San Diego, CA), as Vice President, Clinical Development, for the development of MP4, a pegylated hemoglobin solution for use as an oxygen therapeutic. Since 2016, Dr. Keipert has been employed by PAREXEL International, a clinical services organization where his work does not involve any conflict of interest with the development of Hb or PFC-based oxygen therapeutic agents.